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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,455	12/28/2001	Yasuaki Itoh	56804 (46342)	5636

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	13

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/019,455	Applicant(s) ITOH ET AL.	
	Examin r Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *24 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *41* is/are allowed.

6)☒ Claim(s) *25-40 and 42-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 6/24/03 (Paper No. 10), is acknowledged.

2. Claims 25-46 are pending.

3. Claims 25-46 are under consideration in the instant application.

4. The following new ground of rejections are necessitated by the amendment filed 6/24/03 (Paper No. 10).

5. Claims 32-37 are objected to under 37 CFR § 1.75(c) as being in improper form because a multiple dependent claim cannot depend from two sets of claims drawn to two different features.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 25-40 and 42-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 25-26 are indefinite in the citation of "substantially equivalent" because it is impossible to determine the equivalents of the biological activities in relation to what is being claimed.

It is again suggested that Applicant amend the claims to particularly point out and distinctly claim each cDNA.

B. Claims 32-40 and 44-46 are indefinite for being dependent upon claim 1, which has been canceled.

C. The citation of "base sequence" in claims 31-31 and 44 is ambiguous. While "base sequence" refers to the order of nucleotide bases in a DNA molecule, the art uses "nucleic acid sequence" to refer to the order of nucleotide bases in a DNA molecule.

D. Claim 39 is indefinite in the recitation of the biological activity comprises "induction of cartilage differentiation and induction of proliferation of a cell in which the polypeptide is expressed" (more of). These two biological activities are mutually exclusive in that

they reach opposing endpoints. It is unclear how the same molecule employed to accomplish these mutually exclusive endpoints.

E. Claim 39 is indefinite in the recitation of "and" in lines 3 and 5, the Office recommends the use of the conjunction "or" rather than "and" in listing the species.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 39-40 and 45-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "wherein the biological activity comprises one or more of: expression in cartilage tissue, induction of cartilage differentiation, induction of proliferation of a cell in which the polypeptide is expressed, and binding to an antibody which specifically binds to a polypeptide according to SEQ ID NO: 6, 12, 24, 26, 47 and 49" claimed in claim 39, lines 1-6, the phrase "the polypeptide comprises a label" claimed in claim 45, lines 3-4, and the phrase "a reagent for measuring a biological activity of the polypeptide" claimed in claim 46 represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 6/24/03 points to the specification at pages 7, 13-21 and examples for support for the newly added limitations "wherein the biological activity comprises one or more of: expression in cartilage tissue, induction of cartilage differentiation, induction of proliferation of a cell in which the polypeptide is expressed, and binding to an antibody which specifically binds to a polypeptide according to SEQ ID NO: 6, 12, 24, 26, 47 and 49" as claimed in claim 39, "the polypeptide comprises a label" claimed in claim 45, lines 3-4, and the phrase "a reagent for measuring a biological activity of the polypeptide" claimed in claim 46. However, the specification does not provide a clear support of the newly claimed limitations. The instant claims now recite limitations which were not clearly disclosed in the specification and claims as originally filed.

10. Claims 25-40 and 42-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide sequence of SEQ ID NOS: 24, 6, 26, 12, 49 and 47 their amide or ester or a salt thereof, the nucleic acid of SEQ ID NOS: 23, 4, 25, 10, 48 and 46 encoding the polypeptides, recombinant vector comprising the DNA of SEQ ID NOS:

23, 4, 25, 10, 48 and 46, a method for manufacturing the polypeptide, a kit for screening a compound comprising the polypeptides, and composition comprising the polypeptides, their amide or ester, or a salt thereof.; does not reasonably provide enablement for an isolated polypeptide containing the amino acid sequence represented by SEQ ID NO: 24/6, or containing an amino acid sequence represented by SEQ ID NO:24/6, of which one or more amino acids are (i) deleted, (ii) added, (iii) inserted, (iv) substituted by other amino acids, or containing a combination of the modifications described in (i-iv), and having a biological activity substantially equivalent to that of the polypeptide having the amino acid sequence shown by SEQ ID NO:24, or its amide or ester, or a salt thereof in claims 25 and 26, or an isolated nucleic acid comprising a nucleic acid having a base sequence encoding the polypeptide according to claim 25 in claim 31, a pharmaceutical composition comprising the polypeptide, its amide or ester, or a salt thereof and a pharmaceutical carrier in claim 38, any isolated nucleic acid encoding a polypeptide according to claim 39, in claim 40, any reagent for screening a compound or its salt that promotes or inhibits the activity of the polypeptide or its salt, wherein the polypeptide comprises a label in claim 45, or a kit for screening a compound or its salt that promotes or inhibits the activity of the polypeptide, its amide or ester or a salt thereof comprising the polypeptide or its salt of claim 1, and any reagent for measuring a biological activity of the polypeptide in claim 46. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action, paper No. 8, mailed 2/25/03.

Further, claims 25 and 26 recite amino acid deletion, addition, insertion, and substitution by other amino acids, or containing a combination of these modifications. However, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions, for example, can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2).

Also, at issue is whether or not the claimed composition would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

Furthermore, Claim 45 recite the polypeptide comprises a label, however, the only label the specification discloses is the FLAG label. Claim 46 recite a reagent for measuring a biological activity of the polypeptide, however, the specification fails to provide any reagent for measuring the biological activity. There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various labels and reagents recited in the instant claims

Applicant's arguments, filed 6/24/03 (Paper No. 10), have been fully considered, but have not been found convincing.

Applicant argues that the proteins have a biological activity substantially equivalent to the biological activity of the specifically recited sequence, eg., such as expression in cartilage tissue, ability to induce cartilage differentiation or proliferation of a cell in which the polypeptide is expressed, and ability to bind to an antibody which specifically binds to the specifically recited polypeptides. Applicant concluded that such polypeptides which do not possess such activity do not fall within the scope of the claims.

However, the claims fail to meet the enablement requirement for the "how to make and use" prongs of the U.S.C 112, 1st paragraph. The instant fact pattern fails to indicate that a representative number of deletions, additions, insertions, or combination thereof is disclosed. It well known that the position within the protein's sequence where such amino acid substitutions, for example, can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. The artisan would not know the identity of a reasonable number of representative polypeptides falling within the scope of the instant claim and consequently would not have known how to make them.

Applicant argues regarding the pharmaceutical composition that the Examiner's requirement for a working example is not legally appropriate.

However, as noted previously in paper No. 8, the exemplification in the specification is drawn to the suppressive effect of MLP protein on cartilage differentiation using ATDC5 cells *in vitro* assays. While such *in vitro* assay may provide an indication that particular

compounds/compositions are appropriate to target for *further experimental consideration*. Applicant's disclosure does not appear to have provided the skilled artisan with sufficient guidance and support as how to extrapolate data obtained from *in vitro* assay to the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention.

Applicant further argues that due to the high homology of the polypeptide to MIA/CD-RAP which plays an active role in the formation and maintenance of joints from a physiological aspect. Applicant submits that the art is not unpredictable with respect to this class of proteins and therefore, it would not comprise undue experimentation to make and use the pharmaceutical compositions comprising the polypeptides as recited in the newly added claims.

However, the polypeptide of SEQ ID NO: 24 of the invention is only 66% sequence homology to the MIA/CD-RAP. Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). While the MIA/CD-RAP may play an active role in the formation and maintenance of joints from a physiological aspect, there is no evidence that the claimed compounds would share any one of those different activities.

11. Claims 24-40 and 42-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of the polypeptide sequence of SEQ ID NOS: 24, 6, 26, 12, 49 and 47 their amide or ester or a salt thereof, the nucleic acid of SEQ ID NOS: 23, 4, 25, 10, 48 and 46 encoding the polypeptides, recombinant vector comprising the DNA of SEQ ID NO: 23, 4, 25, 10, 48 and 46, a method for manufacturing the polypeptide, a kit for screening a compound comprising the polypeptides, and composition comprising the polypeptides, their amide or ester, or a salt thereof.

Applicant is not in possession of any isolated polypeptide containing the amino acid sequence represented by SEQ ID NO: 24/6, or containing an amino acid sequence represented by SEQ ID NO:24/6, of which one or more amino acids are (i) deleted, (ii) added, (iii) inserted, (iv) substituted by other amino acids, or containing a combination of the modifications described in (i-iv), and having a biological activity substantially equivalent to that of the polypeptide having the amino acid sequence shown by SEQ ID NO:24, or its amide or ester, or a salt thereof in claims 25 and 26, or an isolated nucleic acid comprising a nucleic acid having a base sequence

encoding the polypeptide according to claim 25 in claim 31, a pharmaceutical composition comprising the polypeptide, its amide or ester, or a salt thereof and a pharmaceutical carrier in claim 38, any isolated nucleic acid encoding a polypeptide according to claim 39, in claim 40, any reagent for screening a compound or its salt that promotes or inhibits the activity of the polypeptide or its salt, wherein the polypeptide comprises a label in claim 45, or a kit for screening a compound or its salt that promotes or inhibits the activity of the polypeptide, its amide or ester or a salt thereof comprising the polypeptide or its salt of claim 1, and any reagent for measuring a biological activity of the polypeptide in claim 46 for the same reasons set forth in the previous Office Action, paper No. 8, mailed 2/25/03.

Applicant's arguments, filed 6/24/03 (Paper No. 10), have been fully considered, but have not been found convincing.

Applicant provides the same argument for enablement.

However the broad brush discussion of making and identifying variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the specific polypeptides of SEQ ID NO: 24, 6, 26, 12, 49 and 47 are disclosed. The specification's general discussion of making and identifying for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants.

Further, there is no described or art-recognized correlation or relationship between the structure of the invention, the secretory polypeptides of SEQ ID NO: 24, 6, 26, 12, 49 and 47 and it's function that is induction of cartilage differentiation, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of variants, wherein the variant has one or more amino acids are deleted, added, inserted, substituted or combination of the these modification which retain the features essential to the instant invention.

12. No claim is allowed

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
September 8, 2003

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